Histochemical Studies on Catecholamines

(with Special Reference to the Paraganglion)

by

SUMIO TOMINAGA

From the 2nd Surgical Division, Kyoto University Medical School
(Director : Prof. Dr. CHUJI KIMURA)
and
Department of Surgery, Shinko Hospital, Kobe
(Director : Dr. TAKASHI HIROSHIGE)

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I. INTRODUCTION

The group of the extra-adrenal chromaffin cells called the "paraganglion" by KOHN [19)20)] is known as the site of deposition and excretion of catecholamines. In addition, the extra-adrenal pheochromocytoma originates from this particular organ. It is generally accepted that, in man, the paraganglion degenerates and disintegrates in early childhood, [15)16)17)40)] but COUPLAND[7)], NAKATA[26)] and YAMAJI[42)] have reported the presence of the paraganglion in adults. With reference to NAKATA and YAMAJI's studies, in the present study, the attempt was made to clarify the function of the paraganglion by the histochemical approach (Chromaffin reaction for catecholamine and TAKAMATSU's potassium tellurite method for MAO).

In addition, further histochemical studies were carried out on the catecholamine metabolism in pheochromocytoma and the lumbar sympathetic ganglion in thromboangitis obliterans (BUERGER's disease).

II. EXPERIMENTAL METHODS

1. Histochemistry of Catecholamine

Chromaffin Reaction (HENLE's modification)[27)]

1) The fresh tissues were fixed in REGAUD's solution (8 volume of 3 per cent potassium bichromate and 2 volume of neutral formalin) for 48 hours.

2) Enbedded in paraffin and sliced.

3) Stained with hematoxylin.

4) Dehydrated and mounted.

With this method, cells which contain noradrenalin and adrenalin are selectively stained dark brownish yellow.

2. Histochemistry of Monoamine oxidase (MAO)

TAKAMATSU's potassium tellurite method[34)35)]

1) Place fresh tissue slices (3 to 5 mm thick) in 30 per cent cold alcohol for 30 to 60 minutes.

2) Then dip the specimen in 1/100 M KCN for 10 to 30 min.

3) Incubate at 37°C for 4 to 5 hours in the equivalent mixture solution composed of 0.1 per cent tyramine, 0.5 per cent potassium · tellurite and 1/15 M phosphate buffer (pH : 7.4).

4) Fix in formalin and make frozen sections. Dip in aurum chloride solution for 30 min. With this procedure, gold substitution is attained.

5) Dip in thiosulfate sodium and then wash.

6) Mount with balsam.

The cells posessing MAO activity are stained in violet blue in color.

III. DISCUSSION OF THESE EXPERINENTAL METHODS

In the present study, the two methods mentioned above were utilized to determine the catecholamine level. The speciality of the adopted methods is discussed here.

In the histochemical approach for studying catecholamine levels, comparative observations between the histochemical activity of catecholamine per se and the activity of MAO, one of the enzymes of the catecholamine metabolism, have been well documented.

1. There are two methods for the histochemical detection of catecholamine itself ; (1) chromaffin reaction and (2) fluorescence method.[11] It is known that the clear-cut findings are not readily obtained with the former method except for the findings of the adrenal medulla and of the small blood vessels. In contrast, the latter method has been generally accepted as the more precise method. In the adrenal medulla and the paraganglion, however, either method gives the very similar results of the activity.[35] Thus the chromaffin reaction was used in the present study for the histochemical detection of catecholamine itself.

2. Although a satisfactory histochemical method for MAO is not known as yet, the potassium tellurite method is considered to be most useful because of the fact that the endogenous dehydrogenase activity, except for MAO, can be abolished with the preliminary treatment using KCN.[35]

It the histochemical detection of MAO, the following two points were investigated. (1) Specificity of MAO to the substrate and (2) grade of the MAO activity affecting the catecholamine metabolism.

MAO has a specificity for adrenalin or noradrenalin in both adrenal medulla and paraganglion because of the fact that these organs are similar in the following two points ; no secretion of serotonin and no toxic amines are found there as in the liver and the kidney.[35][36]

As to the MAO activity affecting catecholamine metabolism, CROUT[9] showed that MAO played a major role, while catechol-o-transferase played a minor role, in the endogenous catecholamine metabolism.

Consequently, the catecholamine levels in the paraganglion and the adrenal medulla are estimated by the chromaffin reaction and the potassium tellurite method.

OKINAKA, UONO and TANABE[29][35][38] found that there were two types of nerve cells distinguishable by the MAO activity ; that is the nuclear positive type and the nuclear negative type. They also found that the former type is of higher adrenergic potency in nature than the latter type. Estimation of the MAO activity in the present study followed

the OKINAKA's results mentioned above.

IV. MATERIALS

1. Rabbit : Laparotomized under intravenous anesthesia (with Nembutal 20 mg/kg) and then were bled to death. The materials were obtained from the retroperitoneal tissues including the abdominal aorta from the origin of the celiac artery to the bifurcation of the iliac artery.

2. Newborn infant : Seven newborn infants of 8 to 10 months gestation, died 2 to 3 days after birth, were used.

The materials were prepared within 6 hours after death with the same procedure as rabbit.

3. Adult : The retroperitoneal tissues were obtained from adult patients who had died of essential hypertension, within 10 hours after death.

4. Materials were obtained at surgery from cases of adrenal pheochromocytoma and extra-adrenal pheochromocytoma.

5. Six cases of BUERGER's disease : The lumbar sympathetic ganglia were obtained surgically. As the control, five lumbar sympathetic ganglia were obtained from adult patients who had died of other diseases, within 6 hours after death.

V. EXPERIMENTS AND RESULTS

1. The microscopic structure of the rabbit paraganglia is shown in Fig. 7 and 8. These paraganglia were adherent to the anterior wall of the abdominal aorta and encapsulated with a thin capsule. Microscopic examination revealed that the epitheroid cells with the vacuoles formed a columnar structure in which the blood vessels were scattered. There was little difference between these findings and those of the adrenal medulla, as shown in Fig. 9. These paraganglia were positive to the chromaffin reaction and also showed the marked MAO activity of the nuclear positive type (Fig. 1).

Histochemical studies were performed on the secretory function of the paraganglion and of the adrenal medulla after administering reserpine or chlorpromazine.

Table 1 Changes of the MAO activity after administration of reserpine

	A-Group	B-Group
Paraganglion	unchanged	decreased
Adrenal medulla	unchanged	decreased

Table 2 Changes of the chromaffin reaction after administration of chlorpromazine

	A-Group	B-Group
Paraganglion	unchanged	decreased
Adrenal medulla	unchanged	decreased

Table 3 Changes of the MAO activity after administration of chlorpromazine

	A-Group	B-Group
Paraganglion	unchanged	decreased
Adrenal medulla	unchanged	decreased

Table 4 Pheochromocytoma

Case Number	1	2
Sex and Age	Female. 39	Female, 28
Location of tumor	adrenal	extra-adrenal
Blood pressure	260-130	200-110
Adrenalin in urine	813μg/day	70.5μg/day
Noradrenalin in urine	959μg/day	300μg/day
VMA in urine	59mg/day	31.8mg/day
Microscopic picture	Atypia(+)	Atypia(+)
Chromaffin reaction	(卅)	(+)
MAO activity	(卄)	(卄)

Symbols indicate : (卅) highest activity
(卄) moderate activity
(+) slight activity

Fig. 1 The paraganglion of rabbit (control)
MAO activity (nuclear positive type) ×400

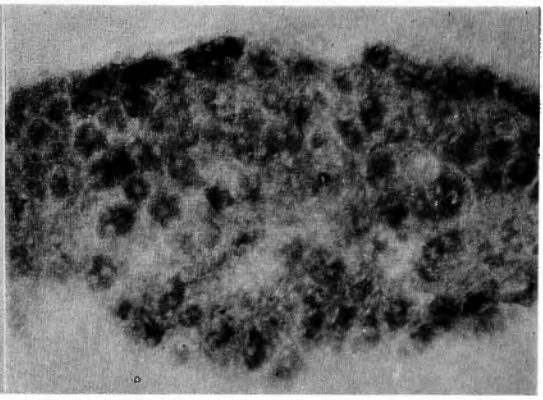


Fig. 2 The paraganglion of rabbit after administration of reserpine
MAO activity (nuclear negative type) ×400

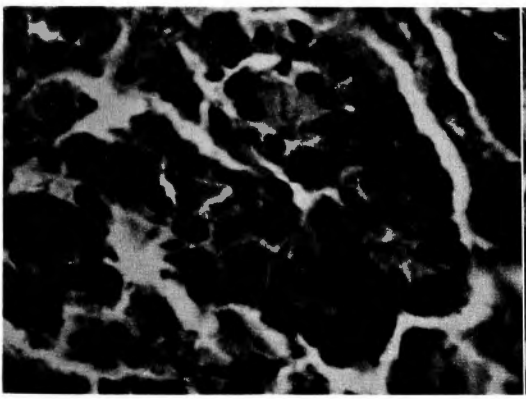


Fig. 3 Adrenal pheochromocytoma
Chromaffin reaction ×400

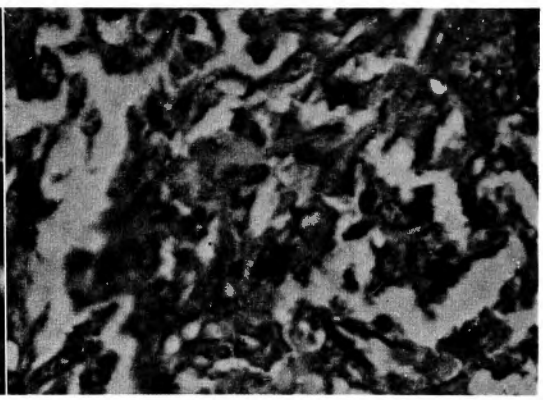


Fig. 4 Extra-adrenal pheochromocytoma
Chromaffin reaction ×400

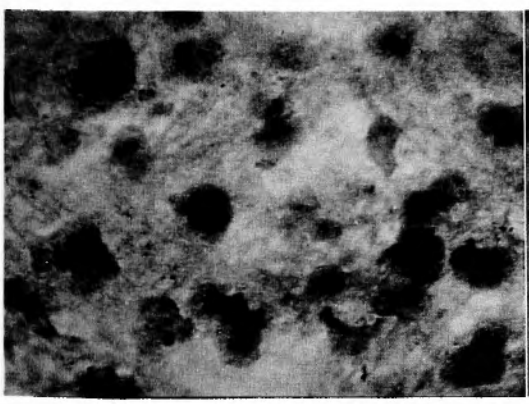


Fig. 5 Lumbar sympathetic ganglion (control)
MAO activity (nuclear positive type) ×400

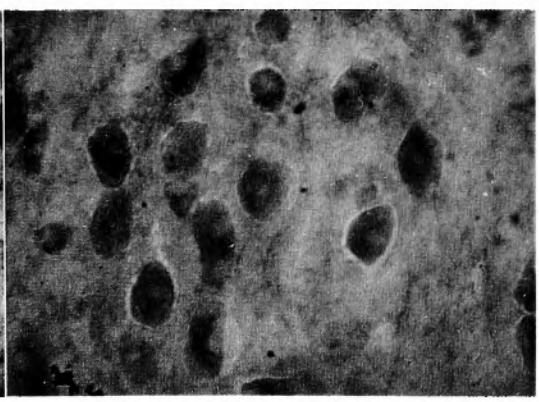


Fig. 6 Lumbar sympathetic ganglion in Buerger's disease
MAO activity (nuclear negative type) ×400

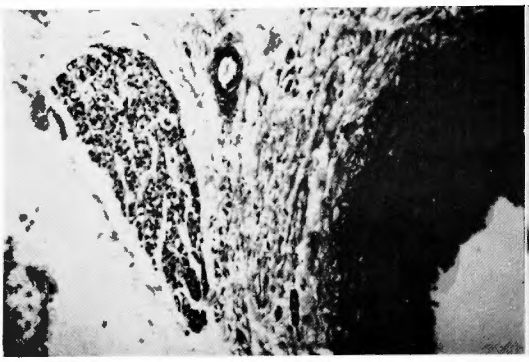


Fig. 7 The paraganglion of rabbit. H .E. × 100

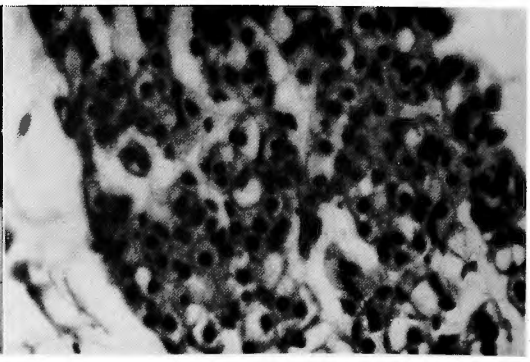


Fig. 8 The paraganglion of rabbit. H. E. × 600

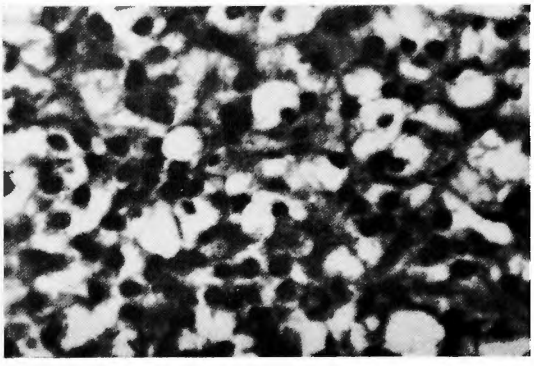


Fig. 9 The adrenal medulla of rabbit. H. E. × 600

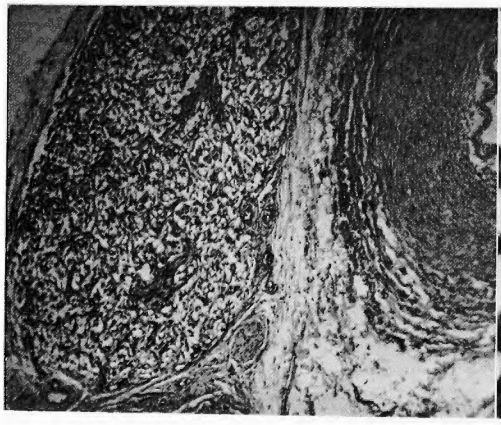


Fig. 10 The paraganglion of newborn infant. H. E. × 100

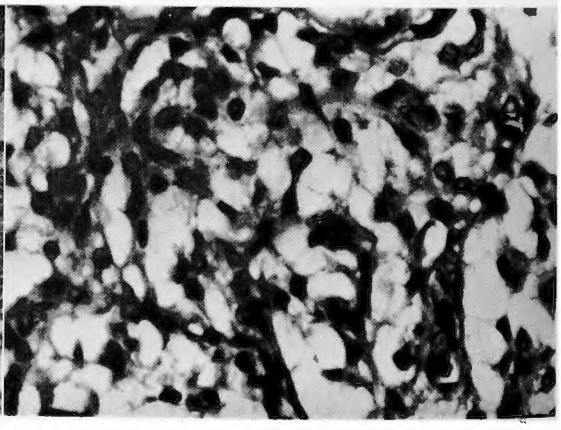


Fig. 11 The paraganglion of newborn infant. H. E. × 600

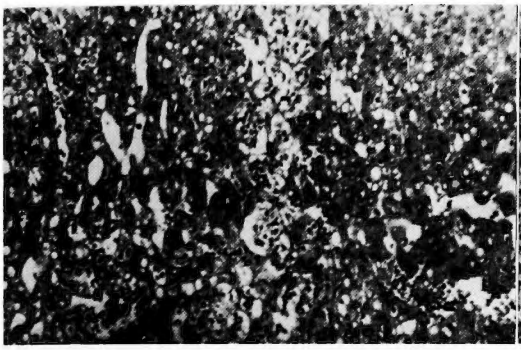


Fig. 12 The adrenal medulla of newborn infant is still premature. H. E. × 100

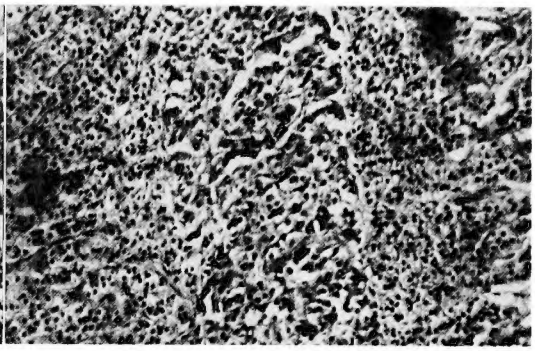


Fig. 13 The adrenal medulla of 3 year old child is well developed. H. E. × 100

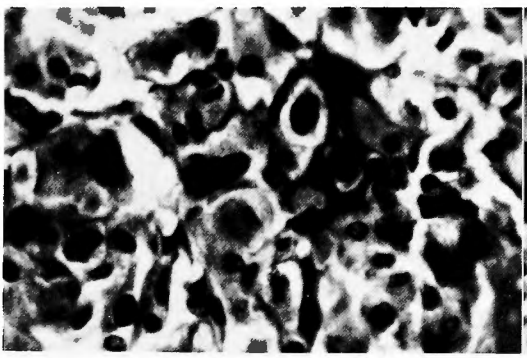


Fig. 14 Adrenal pheochromocytoma. H. E. × 600

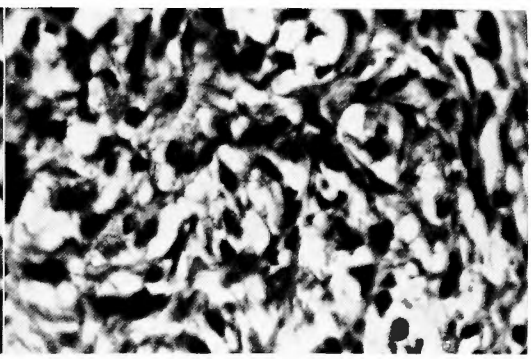


Fig. 15 Extra-adrenal pheochromocytoma. H. E. × 600

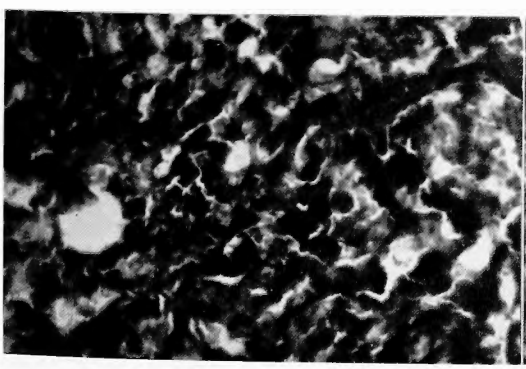


Fig. 16 Adrenal pheochromocytoma. MAO activity. × 150

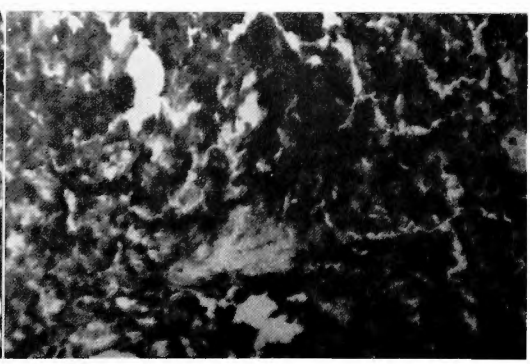


Fig. 17 Extra-adrenal pheochromocytoma. MAO activity. × 150

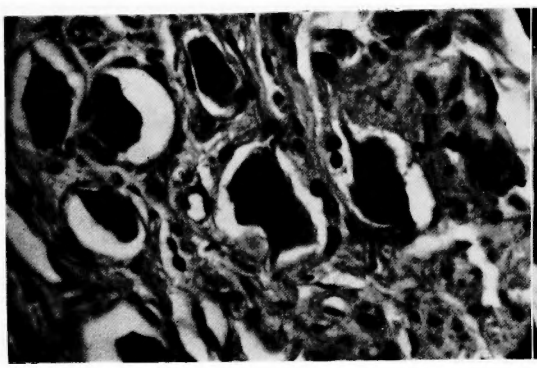


Fig. 18 Lumbar sympathetic ganglion in Buerger's disease. Atrophy of the nerve cell. H. E. ×600

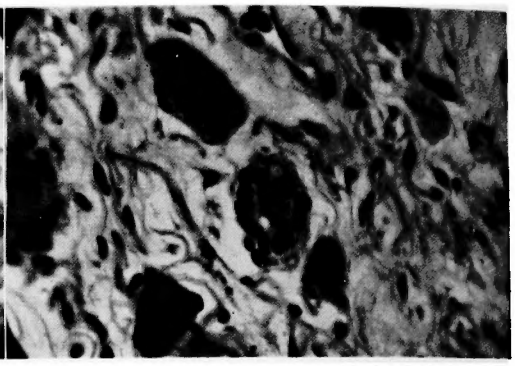


Fig. 19 Neuronophagia. H. E. ×600

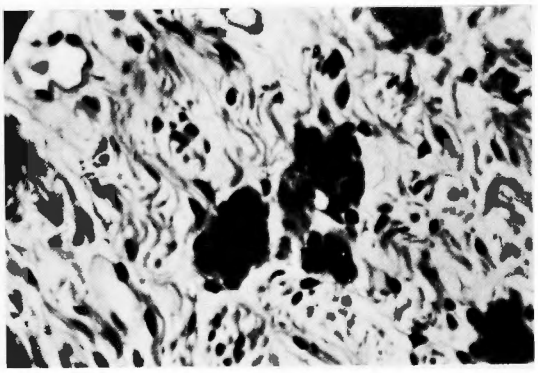


Fig. 20 Neuronophagia. H.E. × 600

1) Reserpine :

A-Group : Five rabbits were used. Five mg per kg of reserpine was given intravenously and the animal sacrificed after 24 hours.

B-Group : Five rabbits were used. The same dosage was given subcutaneously once a day for 7 days and the animal sacrificed 24 hours after the last injection.

As shown in Table 1, the MAO activity of the B-Group showed a marked decrease and nuclear negative type (Fig. 2), on the contrary, that of the untreated Group showed nuclear positive type (Fig. 1).

The MAO activity of the A-Group showed no change.

2) Chlorpromazine : Chlorpromazine was given to rabbits in a dose of 5 mg per kg with the same method as reserpine. Table 2 and 3 indicate that the catecholamine level of the paraganglion and of the adrenal medulla showed a marked decrease in the B-Group in which chlorpromazine was administered for 7 days.

2. A comparative microscopic study was made of the paraganglion and the adrenal medulla in infancy. In the newborn, the paraganglion was located close to the abdominal aorta as shown in Fig. 10. Fig. 11 shows the vacuolar parenchymal cells forming irregular cords and a vascular network. In the adrenal medulla, on the other hand, parenchymal cells are scattered in clumps and these cells invaded into the cortex along the neural fasciculus (Fig. 12).

As seen in Fig. 13, the adrenal medulla of a 3 year old child showed the similar picture to that in adults.

There were no significant differences in the activity of catecholamine and MAO between the paraganglion and the adrenal medulla of the newborn.

3. Materials were obtained from 5 patients who had died of essential hypertension. The retroperitoneal tissues adherent to the abdomial aorta were removed from the level of the superior mesenteric artery to the common iliac artery. The attempt to find paraganglia in these tissues resulted in failure.

4. Comparative studies were performed microscopically and histochemically on each case of adrenal and extra-adrenal pheochromocytomas.

Atypia was more marked in adrenal (Fig. 14) than in extra-adrenal of which picture resembled to the adrenal medulla of adult and the paraganglion of the newborn infant (Fig. 15).

As shown in Fig. 3 and 4, the catecholamine activity of the adrenal was higher than that of the extra-adrenal, while the MAO activity showed no differences between the two (Fig. 16 and 17).

5. BUERGER's disease : Five cases were examined. The MAO activities in the sympathetic ganglia of L_3 and L_4 of the patients with BUERGER's disease were compared with those of patients who died of other diseases. The results showed that the sympathtic ganglion in this disease was the nuclear negative type in MAO activity (Fig. 6), while the ganglion of the control group was the nuclear positive type as seen in the previous report by OKINAKA et al.[29] (Fig. 5).

Moreover, the microscopic findings of the ganglion in this disease showed atrophy of the nerve cells (Fig. 18) and the neuronophagia (Fig. 19 and 20). These findings were consistent with the degeneration of the nerve cells.

VI. DISCUSSION

1. It is generally accepted that the catecholamine level in the various organs is reduced by the administration of reserpine. There are two explanations for the mechanism of the reserpine action in the adrenal medulla : (1) the catecholamine release is accelerated through the central nervous system (sympathetic nervous system)[5][14][25] and (2) catecholamine in the adrenal medulla is reduced by the inhibition of the noradrenalin synthesis from dopamine in the same organ[4][18]. YAMAJI[42] found that the catecholamine activities in the adrenal medulla and the paraganglia are decreased by a single injection of reserpine. In this study, the MAO activities were unchanged with a single injection of reserpine but decreased considerably with the repeated administration for 7 days (Fig. 2). This result indicates that the decrease of the catecholamine activity per se occurs somewhat earlier than that of the MAO activity.

It was also observed that the repeated administration of chlorpromazine for 7 days gave the same results as reserpine.

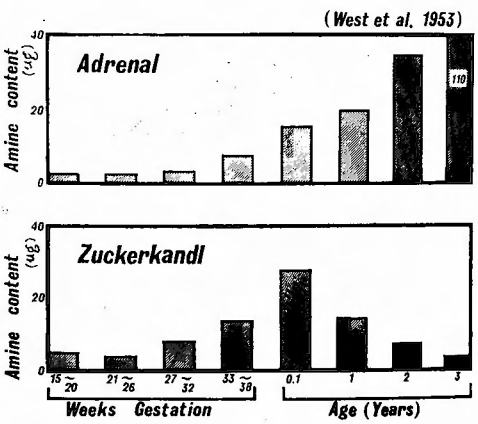
Therefore, the fact that the hypotensors such as reserpine or chlorpromazine decreased the catecholamine level in the chromaffin cells would be available for studying catecholamines as a causal factor of hypertension. It is known that the preventive measures against the excessive secretion of catecholamines in pheochromocytoma is desired because of the

high mortality rate at surgery in this disease.[8)32)33)] Thus, it is reasonable to reduce the catecholamine level as low as possible preoperatively. Based upon this concept, KIMURA[21)] obtained a satisfactory effect by the preoperative administration of propranolol (β-adrenergic blockade). In the present study, the preoperative administration of reserpine or chlorpromazine is suggested.

2. Both adrenal medulla and paraganglion develop from the sympathogonia embryologically. For example, the adrenal medulla is formed from a portion of the sympathogonia which has invaded into the germ of the cortex.[6)16)17)20)] In this paper, various comparisons were made on the adrenal medulla and the paraganglion in the newborn infant. The adrenal medulla is still premature in the newborn infant (Fig. 12), while the adrenal medulla of a 3 year old child is as mature as that of the adult (Fig. 13). On the other hand, it is observed that the paraganglion of the newborn infant is closely adherent to the blood vessels and the parenchymal cells are well developed (Fig. 10 and 11).

WEST et al.[40)41)] carried out the comparative studies on the function of the so-called "ZUCKERKANDL Organ" (paraganglion) and the adrenal medulla in infancy. Table 5 shows that the adrenal medulla begins to function adequately one year after birth, while the "ZUCKERKANDL Organ" maximally functions in the newborn infant and then gradually decreases until 4 years of age. When considering the physiological findings mentioned above and the histological findings of the present study, it may be assumed that the adrenal medulla is premature in the nowborn infant and its function is compensated by the paraganglion which degenerates inversely parallel with development of the adrenal medulla. According to IVANOFF[15)] and IWANOW[16)17)], the degeneration takes place in the paraganglin around 2 years of age. WEST[40)] states that there is no function in the "ZUCKERKANDL Organ" (paraganglion) in adults.

Table 5



On the contrary, COUPLAND[7)], NAKATA[26)] and YAMAJI[42)] observed that the paraganglia existed without degeneration in adults.

3. In continued existence of the paraganglion in adult, hyperfunction may occur aside from extra-adrenal pheochromocytoma. The hyperfunction of the paraganglion may be observed in angiospasm since the paraganglion is the secreting organ of noradrenalin. Thus, essential hypertension and BUERGER's disease are worthwhile to be considered here.

KIMURA and NAKATA[22)26)] reported that the resection of the paraganglia was effective in BUERGER's disease.

As to the pathogenesis of essential hypertension, it may be related to various factors including neural, endocrine, nephrotic or hereditary etc.

There is much controversy concerning the relationship of catecholamine to essential hypertension. OKAMOTO and AOKI[28)] succeeded in producing spontaneously hypertensive rats in which conditions were similar to those of essential hypertension in man in view

of the pathogenesis and the hereditary pattern. TABEI[37] found that there was a marked increase of the area occupied by the noradrenalin-storing cell islets in the adrenal medulla in these rats.

In man, some patients with essential hypertension showing the increased urinary excretion of catecholamine have been experienced.[12][31][39] On the other hand, there were also some cases with the preoperative diagnosis of pheochromocytoma in whom no tumor of this kind was actually found on operation.[43] Therefore, it cannot be denied that there might exist a type of hypertension associated with the increased urinary excretion of catecholamine, besides pheochromocytoma.

In the present study it was found that the hypotensors such as reserpine and chlorpromazine induced a decrease of the catecholamine level in the adrenal medulla and the paraganglion. This suggests that there may be some relationship between these chromaffin cells and hypertension.

Viewed from these points, the effort was made to clarify the pathophysiology of the paraganglia in autopsy cases of essential hypertension by the histochemical methods, but no positive finding could be obtained. Further investigation of this problem must be continued.

4. The paraganglion is known as the organ from which the pheochromocytoma arises. YOSHIUE[44] reported that 18 cases (23 per cent) of 79 pheochromocytomas were extra-adrenal in origin. It has been known that there is no definite correlation between the catecholamine level in the tumor and that in urine[23]. CROUT and SJOERDSMA[10] estimated the urinary excreted portion of catecholamine and its metabolite (VMA) from total cathecolamines in the tumor. The results ranged from 1.4 to 22 per cent.

The pathogenesis of the hypertension in pheochromocytoma cannot be explained only by the elevated levels of noradrenalin and adrenalin. For knowledge of this pathogenesis, the biosynthesis and metabolism of catecholamine should be clarified.[30] Thus in this paper the MAO activity concerned with the endogenous catecholamine metabolism was studied.

Results of the comparative studies on the extra-adrenal pheochromocytoma and the adrenal type is shown in Table 4. In the case of extra-adrenal pheochromocytoma, catecholamine and VMA in urine are less with the concomitant fall of blood pressure than in the adrenal type. The cause of this fact may be related to the following, (1) the catecholamine activity per se in extra-adrenal pheochromocytoma is lower than that of the adrenal type (Fig. 3 and 4) and (2) the MAO activity has no difference between two cases (Fig. 16 and 17). These findings indicate an abnormal catecholamine metabolism.

5. Since ADSON and BROWN[1] observed the vasodilatation after lumbar sympathectomy in adults, sympathectomy has become prevalent in the peripheral arteriopathy.

KUMAMOTO[24] and HIRAKOU[13] found a marked degeneration of the nerve cells in the resected sympathetic ganglia in BUERGER's disease and suggested that the degeneration might indicate a pathogenesis of BUERGER's disease.

On the other hand, AKIYAMA[2] stated that evidences of the degeneration were scarcely observed in diseases of the peripheral artery and that there was a dense population of the nerve cells, suggesting a hyperkinetic status of the sympathetic ganglia in these diseases.

In the present study, it was found that there were degenerative changes in the lumbar sympathetic ganglia in BUERGER's disease as indicated in Fig. 18, 19 and 20. The MAO activity in the ganglia was studied in an attempt to obtain more knowledge of the function

of the ganglia. The results showed that the MAO activity in BUERGER's disease was lower than that in the control (Fig. 5) and indicated the nuclear negative type (Fig. 6). In conclusion, the lumbar sympathetic ganglia in this disease are poor in adrenergic nature and hypokinetic. If sympathetic ganglia played an important role for the pathogenesis of BUERGER's disease, the function of the ganglia should have been hyperkinetic. In other words, the sympathetic ganglia have no intrinsic roie in the pathogenesis of BUERGER's disease. Sympathectomy is only a intercepting procedure of sympathetic nervous impulses.

VII. SUMMARY

In the present study, the paraganglion, pheochromocytoma and the lumbar sympthetic ganglion in BUERGER's disease were investigated histochemically.

1. Reserpine or chlorpromazine was administered to rabbits for studying the secretory function of the paraganglion. There was a decrease of catecholamine level in both paraganglion and adrenal medulla. From this result, the preoperative administration of these medicines in pheochromocytoma was advocated for the purpose of lowering the catecholamine level in the tumor and preventing the patients from the hypertensive crisis.

2. In the newborn infant, the adrenal medulla is still premature, while the paraganglion is well-developed. Thus the paraganglion in the newborn infant appears to carry out a compensatory function on the adrenal medulla.

3. The paraganglion, a noradrenalin secreting organ, is certified in human adult as in newborn infant. This fact may imply the existence of the pathological condition which is concerned with the angiospasm. Thus the relationship of the paraganglion to essential hypertension was studied. However, satisfactory results have not been obtained.

4. It was found that the catecholamine activity of extra-adrenal pheochromocytoma was lower than that in the adrenal type and the MAO activity has no difference between the two cases.

This result, an abnormal catecholamine metabolism, may be related to the difference of the blood pressure value between these two cases.

5. Degenerative changes of the nerve cells were observed in the lumbar sympathetic ganglion of the patient with BUERGER's disease. In accordance with these findings, the MAO activity of its ganglion was lower than that in the control group. Accordingly, it was suggested that the function of the lumbar sympathetic ganglion in BUERGER's disease was hypokinetic.

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(*written in Japanese)

和文抄録

カテコールアミンの組織化学
(パラガングリオンを中心として)

京都大学医学部外科学教室第2講座(指導:木村忠司教授)
神鋼病院外科(院長:弘重充博士)

冨永純男

Kohnによりパラガングリオンと名付けられた副腎外クロム親和細胞群は,副腎髄質及びアドレナリン性神経以外のカテコールアミンの貯蔵分泌場所として,又副腎外褐色細胞腫の発生母地として存在する.

しかし,人間にあつては,幼児期すでに,変性,退化してしまうものと一般に考えられていた.これに対し,Coupland及び教室の仲田,山地は成人に於いても,パラガングリオンの在在することを証明した.

著者は,仲田,山地につづいて,組織化学的方法(①カテコールアミンに対する重クロム酸カリ法 ②カテコールアミン分解酵素たるモノアミンキシターゼ(MAO)に対する亜テルル酸カリ法)を用いて,パラガングリオンの機能とその存在意義につき追求した.

更に,この組織化学的方法を用いて,褐色細胞腫及びBuerger氏病に於ける腰部交感神経節のカテコールアミン代謝についても追求した.その結果,

(1) パラガングリオンの分泌活動性証明のため,レセルピン,クロールプロマジンをウサギに投与し,パラガングリオン,副腎髄質のカテコールアミンレベルの低下をみとめた.

褐色細胞腫の手術に際し,これ等薬剤を術前投与し,術中の高血圧発作の予防を計るべきことを主張した.

(2) 新生児に於いては,副腎髄質の発育は未成熟で,これに対しパラガングリオンは,一つの完成された細胞群を形成している.即ち新生児に於いては,パラガングリオンが副腎髄質の代償機能を営んでいると考える.

(3) 成人に於いて,ノルアドレナリンを分泌するパラガングリオンが存在する時,Angiospasmと結びついた病態の存在が考えられる.そこで,本態性高血圧症との関係につき追求したが結論を得なかつた.

(4) 褐色細胞腫(副腎性1例,副腎外性1例)を組織化学的に追求した.腫瘍のカテコールアミン自身の活性は,副腎外性のものは副腎性のものより著明に低くかつた.一方カテコールアミン分解酵素たるMAO活性には両者間に於いて差を認めなかつた.このような一種の代謝経路に於ける異常が,褐色細胞腫に於ける高血圧レベルを決める一因となり得るのではないかと考える.

(5) Buerger氏病腰部交感神経節には,神経細胞の変性所見をみとめ,それに伴つて,又神経節MAO活性は,対照群と比較して著明に低下していた.即ちBuerger氏病にあつては,腰部交感神経節はhypokineticであることを認めた.